

Application No.: 09/993,844  
Amdt. Dated: October 1, 2004  
Reply to Office Action Dated: June 23, 2004



Attorney Docket No. NRK.10026  
Page 8 of 10

**Amendments to the Drawings:**

Please replace Figures 1, 2, 3, 4, 7, 8, 9, 10, and 11 with the following replacement figures that are attached hereto: Figures 1A, 1B, and 1C; 2A, 2B, 2C, and 2D; 3A and 3B; 4A, 4B, and 4C; 7A and 7B; 8A, 8B, and 8C; 9A, 9B, and 9C; 10A, 10B, 10C, 10D, and 10E; and 11A, 11B, 11C, 11D, 11E, and 11F.

No new matter has been added to the Figures.

# FIGURE 1A

## Human G Protein Coupled Receptor Family

(Receptors known as of January, 1999)

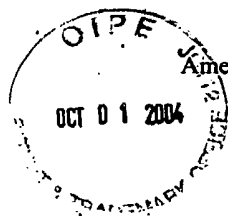
| CLASS   | LIGAND | NUMBER | TISSUE                   | PHYSIOLOGY               | THERAPEUTICS                           |
|---|--------|--------|--------------------------|--------------------------|--|
| •Class I<br>Rhodopsin like                      |        |        |                          |                          |  |
| •Amine  |        |        |                          |                          |  |
| •Acetylcholine<br>(muscarinic & nicotinic)      |        | 5      | Brain, Nerves, Heart     | Neurotransmitter         | Acuity, Alzheimer's                    |
| •Adrenoceptors                                  |        |        |                          |                          |  |
| •Alpha Adrenoceptors                            |        | 6      | Brain, Kidney, Lung      | Gluconeogenesis          | Diabetes, Cardiovascular               |
| •Beta Adrenoceptors                             |        | 3      | Kidney, Heart            | Muscle Contraction       | Cardiovascular, Respiratory            |
| •Dopamine                                       |        | 5      | Brain, Kidney, GI        | Neurotransmitter         | Cardiovascular, Parkinson's            |
| •Histamine                                      |        | 2      | Vascular, Heart, Brain   | Vascular Permeability    | Anti-inflammatory, Ulcers              |
| •Serotonin (5-HT)                               |        | 16     | Most Tissues             | Neurotransmitter         | Depression, Insomnia, Analgesic        |
| •Peptide  |        |        |                          |                          |  |
| •Angiotensin                                    |        | 2      | Vascular, Liver, Kidney  | Vasoconstriction         | Cardiovascular, Endocrine              |
| •Bradykinin                                     |        | 1      | Liver, Blood             | Vasodilation,            | Anti-inflammatory, Asthma              |
| •C5a anaphylatoxin                              |        | 1      | Blood                    | Immune System            | Anti-inflammatory                      |
| •Fmet-leu-phe                                   |        | 3      | Blood                    | Chemoattractant          | Anti-inflammatory                      |
| •Interleukin-8                                  |        | 1      | Blood                    | Chemoattractant          | Anti-inflammatory                      |
| •Chemokine                                      |        | 6      | Blood                    | Chemoattractant          | Anti-inflammatory                      |
| •Orexin   |        | 2      | Brain                    | Fat Metabolism           | Obesity                                |
| •Nociceptin                                     |        | 1      | Brain                    | Bronchodilator, Pain     | Airway Diseases, Anesthetic            |
| •CCK (Gastrin)                                  |        | 2      | Gastrointestinal         | Motility, Fat Absorption | Gastrointestinal, Obesity, Parkinson's |
| •Endothelin                                     |        | 2      | Heart, Bronchus, Brain   | Muscle Contraction       | Cardiovascular, Respiratory            |
| •Melanocortin                                   |        | 5      | Kidney, Brain            | Metabolic Regulation     | Anti-inflammatory, Analgesics          |
| •Neuropeptide Y                                 |        | 5      | Nerves, Intestine, Blood | Neurotransmitter         | Behavior, Memory, Cardiovascular       |
| •Neurotensin                                    |        | 1      | Brain,                   | CNS                      | Cardiovascular, Analgesic              |
| •Opioid   |        | 3      | Brain,                   | CNS                      | Depression, Analgesic                  |
| •Somatostatin                                   |        | 5      | Brain, Gastrointestinal  | Neurotransmitter         | Oncology, Alzheimer's                  |
| •Tachykinin<br>(Substance P, NKA <sub>1</sub> ) |        | 3      | Brain Nerves             | Neurohormone             | Depression, Analgesic                  |

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Response to Office Action dated June 23, 2004

Amendment under 37 C.F.R. § 1.116 filed October 1, 2004

## REPLACEMENT SHEET



REPLACEMENT SHEET

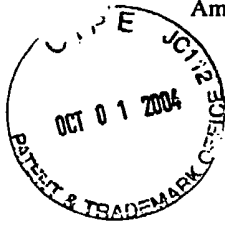


FIGURE 1B

|  |          |                                |                      |                                       |
|--|----------|--------------------------------|----------------------|---------------------------------------|
| •Thrombin                                  | 3        | Platelets, Blood Vessels       | Coagulation          | Anti-coagulant, Anti-inflammatory     |
| •Vasopressin-like                          | 4        | Arteries, Heart, Bladder       | Water Balance        | Anti-diuretic, Diabetic Complications |
| •Galanin                                   | 1        | Brain, Pancreas                | Neurotransmitter     | Analgesics, Alzheimer's               |
| •Hormone protein                           |          |                                |                      |                                       |
| •Follicle stimulating hormone              | 1        | Ovary, Testis                  | Endocrine            | Infertility                           |
| •Lutropin-choriogonadotropic               | 1        | Ovary, Testis                  | Endocrine            | Infertility                           |
| •Thyrotropin                               | 1        | Thyroid                        | Endocrine            | Thyroidism, Metabolism                |
| •(Rhod)opsin                               |          |                                |                      |                                       |
| •Opsin                                     | 5        | Eye                            | Photoreception       | Ophthalmic Diseases                   |
| •Olfactory                                 | 4(-1000) | Nose                           | Smell                | Olfactory Diseases                    |
| •Prostanoid                                |          |                                |                      |                                       |
| •Prostaglandin                             | 5        | Arterial, Gastrointestinal     | Vasodilation, Pain   | Cardiovascular, Analgesic             |
| •Lysophosphatidic Acid                     | 2        | Vessels, Heart, Lung           | Inflammation         | Cancer, Anti-Inflammatory             |
| •Sphingosine-1-phosphate                   | 2        | Most Cells                     | Cell proliferation   | Cancer                                |
| •Leukotriene                               | 1        | White Blood Cells, Bronchus    | Inflammation         | Asthma, Rheumatoid Arthritis          |
| •Prostacyclin                              | 1        | Arterial, Gastrointestinal     | Platelet Regulation  | Cardiovascular                        |
| •Thromboxane                               | 1        | Arterial, Bronchus             | Vasoconstriction     | Cardiovascular, Respiratory           |
| •Nucleotide-like                           |          |                                |                      |                                       |
| •Adenosine                                 | 4        | Vascular, Bronchus             | Multiple Effects     | Cardiovascular, Respiratory           |
| •Purinoreceptors                           | 4        | Vascular, Platelets            | Relaxes Muscle       | Cardiovascular, Respiratory           |
| •Cannabis                                  | 2        | Brain                          | Sensory Perception   | Analgesics, Memory                    |
| •Platelet activating factor                | 1        | Most Peripheral Tissues        | Inflammation         | Anti-inflammatory, Anti-asthmatic     |
| •Gonadotropin-releasing hormone like       |          |                                |                      |                                       |
| •Gonadotropin-releasing hormone            | 1        | Reproductive Organs, Pituitary | Reproduction         | Prostate Cancer, Endometriosis        |
| •Thyrotropin-releasing hormone             | 1        | Pituitary, Brain               | Thyroid Regulation   | Metabolic Regulation                  |
| •Growth hormone- inhibiting factor         | 1        | Gastrointestinal               | Neuroendocrine       | Oncology, Alzheimer's                 |
| •Melatonin                                 | 1        | Brain, Eye, Pituitary          | Neuroendocrine       | Regulation of Circadian Cycle         |
| •Secretin                                  | 1        | Gastrointestinal, Heart        | Digestion            | Obesity, Gastrointestinal             |
| •Calcitonin                                | 1        | Bone, Brain                    | Calcium Resorption   | Osteoporosis                          |
| •Corticotropin releasing factor/lurocortin | 1        | Adrenal, Vascular, Brain       | Neuroendocrine       | Stress, Mood, Obesity                 |
| •Gastric inhibitory peptide (GIP)          | 1        | Adrenals, Fat Cells            | Sugar/Fat Metabolism | Diabetes, Obesity                     |
| •Glucagon                                  | 1        | Liver, Fat Cells, Heart        | Gluconeogenesis      | Cardiovascular                        |

•Class II  
 Secretin like

## REPLACEMENT SHEET



## FIGURE 1C

|  |   |                               |                    |                                   |
|--|---|-------------------------------|--------------------|-----------------------------------|
| •Glucagon-like Peptide 1 (GLP-1)         | 1 | Pancreas, Stomach, Lung       | Gluconeogenesis    | Cardiovascular, Diabetes, Obesity |
| •Growth hormone-releasing hormone        | 1 | Brain                         | Neuroendocrine     | Growth Regulation                 |
| •Parathyroid hormone                     | 1 | Bone, Kidney                  | Calcium Regulation | Osteoporosis                      |
| •PACAP                                   | 1 | Brain, Pancreas, Adrenals     | Metabolism         | Metabolic Regulation              |
| •Vasoactive intestinal polypeptide (VIP) | 1 | Gastrointestinal              | Motility           | Gastrointestinal                  |
| •Metabotropic Glutamate                  | 7 | Brain                         | Sensory Perception | Hearing, Vision                   |
| •GABA <sub>A</sub>                       | 1 | Brain                         | Neurotransmitter   | Mood Disorders                    |
| •Extracellular Calcium Sensing           | 1 | Parathyroid, Kidney, GI Tract | Calcium Regulation | Cataracts, GI Tumors              |

•ClassIII



REPLACEMENT SHEET  
**FIGURE 2A**

**G protein-coupled receptors:**

(Division into Class A

Or Class B)

1. **A1 adenosine receptor [Homo sapiens].** ACCESSION AAB25533  
npivyaf riqkfrvtfl kiwndhfrqc pappidedlp eerpdd  
Class A
2. **adrenergic, alpha -1B-, receptor [Homo sapiens].** ACCESSION NP\_000670  
npiiypc sskefkrafv rilgcqcrgr grrrrrrrr lggcaytyrp wtrggslers qsrkdsldds gscslgsqrt  
lpsaspspgy lgrgappve lcafepwkap gallspape ppgrgrhds gplftklit epespqtdgg asnggceaaa  
dvangpggfk snmplapgqf  
Class A
3. **adrenergic receptor alpha-2A [Homo sapiens].** ACCESSION AAG00447  
npviytifn hdfrrafkki lcrgrkriv  
Class A
4. **alpha-2B-adrenergic receptor - human.** ACCESSION A37223  
npviytifn qdfrrafri lcrpwtqaw  
Class A
5. **alpha-2C-adrenergic receptor - human.** ACCESSION A31237  
npviytfvn qdfrrafski lfrmrgrf q  
Class A
6. **beta-1-adrenergic receptor [Homo sapiens].** ACCESSION NP\_000675  
npiiycrs pdrfkafqgl lccarraar rhathgdrpr asgclarpqp ppsgaasdd ddddvvgatp parllepwag  
cnggaaadsd ssldepcrpg faseskv  
Class A
7. **beta-2 adrenergic receptor.** ACCESSION P07550  
npliyrcsp dfriaqell clrrsslkay gngyssngnt 361 geqsgyhveq ekenklced lpgtedfvgh qgtvpsdnid  
sqgrncstnd sll  
Class A
8. **dopamine receptor D1 [Homo sapiens].** ACCESSION NP\_000785  
npii yafnadfrka fstllgcyl cpattnaiet vsinnngaam fsshheprgs iskecnlyvl iphavgsedd  
lkkeeaagia rpleklspal svildytdv slekiqpitq ngqhpt  
Class A
9. **D(2) dopamine receptor.** ACCESSION P14416  
npiiyttfn iefrkafiki lhc  
Class A



REPLACEMENT SHEET

**FIGURE 2B**

10. **d3 dopamine receptor - human. ACCESSION G01977**  
np viyttfnief rkafilkilsc  
Class A
11. **dopamine receptor D4 - human. ACCESSION DYHUD4**  
npviyfv fnaefmvfr kalracc  
Class A
12. **dopamine receptor D5 - human. ACCESSION DYHUD5**  
npviya fnadfqqvfa qlgcsfhcs rtpvetvnis nelisynqdi vfheiaaay ihmmpnavtp gnrevdndec  
egpfdrmfqi yqtspdgdpv aesvweldec geisldkitp ftpngfh  
Class A
13. **muscarinic acetylcholine receptor M1 [Homo sapiens]. ACCESSION NP\_000729**  
nrmcyal cnkafdrtdfr lllcrwdkr rwrkiplkpg svhrtpsrgc  
Class A
14. **muscarinic acetylcholine receptor M2 [Homo sapiens]. ACCESSION NP\_000730**  
npacy alcnatfkkt fkhllmchyk nigatr  
Class A
15. **muscarinic acetylcholine receptor M3 [Homo sapiens]. ACCESSION NP\_000731**  
n pvcyalcnkt frttfkmlll cqdckkkrrk qqyqqrsqi fhkrapeqal  
Class A
16. **muscarinic acetylcholine receptor M4 [Homo sapiens]. ACCESSION NP\_000732**  
npa cyalcnatfk ktrfhlllcq yrnigtar  
Class A
17. **m5 muscarinic receptor. locus HUMACHRM ACCESSION AAA51569**  
npicyalcnr tfrktfkml lcrwkkkkve eklywqgnsk lp  
Class A
18. **5-hydroxytryptamine (serotonin) receptor 1A [Homo sapiens]. ACCESSION BAA90449**  
npviy ayfknkdfqna fkkiikckf  
Class A
19. **5-hydroxytryptamine (serotonin) receptor 1B [Homo sapiens]. ACCESSION BAA94455**  
npiiyt msnedfkqaf hklirfkets  
Class A
20. **5-hydroxytryptamine (serotonin) receptor 1E [Homo sapiens]. ACCESSION BAA94458**  
n pllytsfnd fklafkkliir cre  
Class A

REPLACEMENT SHEET  
**FIGURE 2C**



21. **OLFACTORY RECEPTOR 6A1. ACCESSION O95222**  
npiiyclrnq evkralccil hlyqhqpdp kkgsmv  
**Class A**
22. **OLFACTORY RECEPTOR 2C1. ACCESSION O95371**  
npliy tlmmevkga lrrllgkgre vg  
**Class A**
23. **angiotensin receptor 1 [Homo sapiens]. ACCESSION NP\_033611**  
npl fyglgkfk ryflqlkkyi ppkakshsnl sfkmsflsy psdnvssstk kpapcfeve  
**Class B**
24. **angiotensin receptor 2 [Homo sapiens]. ACCESSION NP\_000677**  
npflycf vgnrfqqklr svfrvpitwl qgkresmscr kssslremet fvs  
**Class B**
25. **interleukin 8 receptor beta (CXCR2) [Homo sapiens]. ACCESSION NM\_001557**  
NPLYAFIGQKFRHGLLKILAIHGLISKDSLKPDSRPSFVGSSSGHTSTTL  
**Class B**
26. **cx3c chemokine receptor 1 (cx3cr1) (fractalkine receptor)**  
ACCESSION P49238  
np liyafagekf rrylyhlygk clavlgrsv hvdffssesq rsrhgsvlss nftyhtsdgd allll  
**Class B**
27. **neurotensin receptor - human. ACCESSION S29506**  
n pilynlvsan frhiflatla clcpvwrrr krpafsrkad svssnhflss natretly  
**Class B**
28. **SUBSTANCE-P RECEPTOR (SPR) (NK-1 RECEPTOR) (NK-1R). ACCESSION P25103**  
npiiyccldn rfrlgfkhafrccpfsisagd yeglemkstr ylqtqgsvyk vsrletfistfvgaheepe dgpkatpssl  
dltsncssrs dsktmtesfs fssnvl  
**Class B**
29. **vasopressin receptor type 2 [Homo sapiens]. ACCESSION AAD16444**  
npwiyasfss svsselsll ccargtrpps lgpqdescff asslakdts s  
**Class B**
30. **thyrotropin-releasing hormone receptor - human. ACCESSION JN0708**  
npviy nlmsqkfraa frklcnckqk ptekpanysv alnysvikes dhfstelddi tvtdtlysat kvsfddtcla sevsfsqs  
**Class B**
31. **oxytocin receptor - human. ACCESSION A55493**  
npwiymlftghlfhel vqrfllccsas ylkgrlget saskksnsss fvlsrshsssq rscsqpsta  
**Class B**

REPLACEMENT SHEET

FIGURE 2D



32. **neuromedin U receptor [Homo sapiens].** ACCESSION AAG24793  
npvylslmssrfretfqealcigacchrlprhsshslsrmttgstlcdvsglsgswvhplagndgpeaqgetdps  
**Class B**
33. **gastrin receptor.** ACCESSION AAC37528  
nplvy cfmhrrfrqa cletcarcep rpprarpral pdedpppsi aslsrlytt isflgpg  
**Class B**
34. **galanin receptor 3 [Homo sapiens].** ACCESSION 10879541  
nplv yalasrhfra rfrlwpcgr rrrhraral rrvrpassgp pgcpgdarps grllagggqg pepregpvhg geaargpe  
**Class A**
35. **edg-1 - human.** ACCESSION A35300  
npiiy tltnkemrra firimsckc psldsagkfk rpiiagmefs rksdnnshp 361 qkdegdnpet imssgnvnss s  
**Class A**
36. **central cannabinoid receptor [Homo sapiens].** ACCESSION NP\_057167  
npiiyalr skdlrhafis mfpscegtaq pldnsmgdsd clkhannaa svhraesci kstvkiaevt msvstdtsae al  
**Class A**
37. **delta opioid receptor - human.** ACCESSION I38532  
npvlyaf ldenfkrcfr qlcrkpcgr dpssfsrpre atarervtac tpsdpggggr aa  
**Class A**
38. **proteinase activated receptor 2 (PAR-2) human.** ACCESSION P55085  
dpfvyyfvshdfirdhaknallersvrtvkqmqvsltskkhsrksssysssttvktsy  
**Class A**
39. **vasopressive intestinal peptide receptor (VIPR) rat.** ACCESSION NM\_012685  
NGEVQAE LRRKWRRWHLQGV LGWSSKSQHPWGG SNGATCSTQV SMLTRVSPSARR  
SSSFQAEVSLV  
**Class B**



REPLACEMENT SHEET



**FIGURE 3A**

**Human V2R DNA (nucleotides encoding the last 29 amino acids of the V2R and the adjacent stop codon):**

**gcccggggacgcacccccaccagcctgggtccccaagatgagtcctgcaccaccgccagtcct  
ccctggccaaggacattcatcgtga**

**FIGURE 3B**

**PCR amplified human V2R DNA fragment:**

**gcggccgcacggggacgcacccccaccagcctgggtccccaagatgagtcctgcaccaccgcc  
agtcctccctggccaaggacattcatcgtgaagatctccgcggtctaga**

\*Additions and changes to the V2R DNA are underlined.

\*The Sma I (cccggg) restriction enzyme site (underlined in Fig. 3A) was eliminated in the amplified DNA fragment by changing a cytosine to an adenine.

\*A Not I restriction site (gcggccgc) was incorporated into the amplified DNA fragment by adding 6 nucleotides (gcggcc) to the 5' end of the V2R DNA.

\*Bgl II (agatct), Sac II (ccgcgg), and Xba I (tctaga) restriction enzyme sites were added to the 3' end of the V2R DNA.

REPLACEMENT SHEET



FIGURE 4A

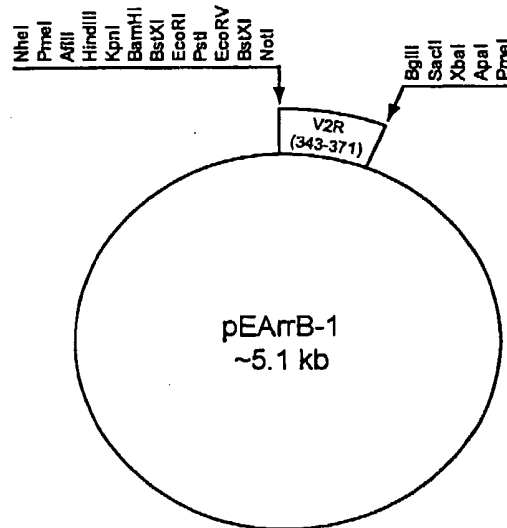


FIGURE 4B

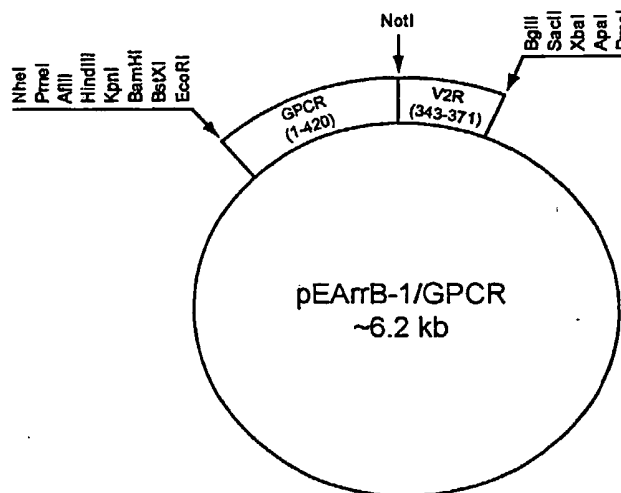


FIGURE 4C

...AAARGRTPPSLGPQDESCTTASSSLAKDTSS

REPLACEMENT SHEET



FIGURE 7B

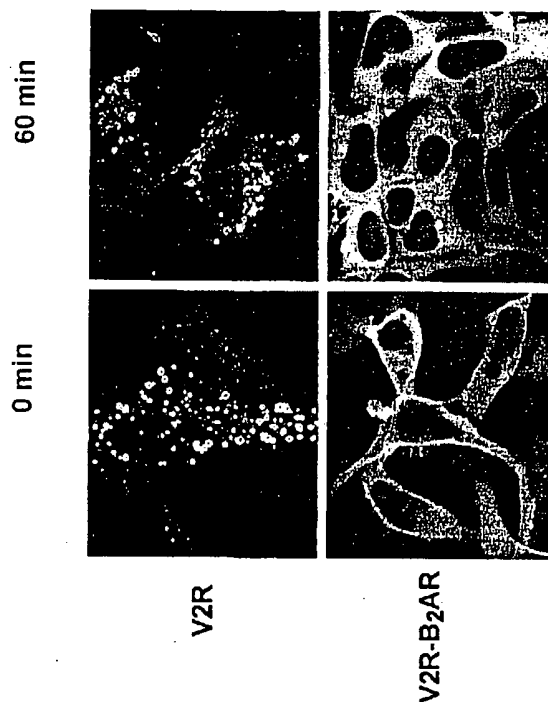
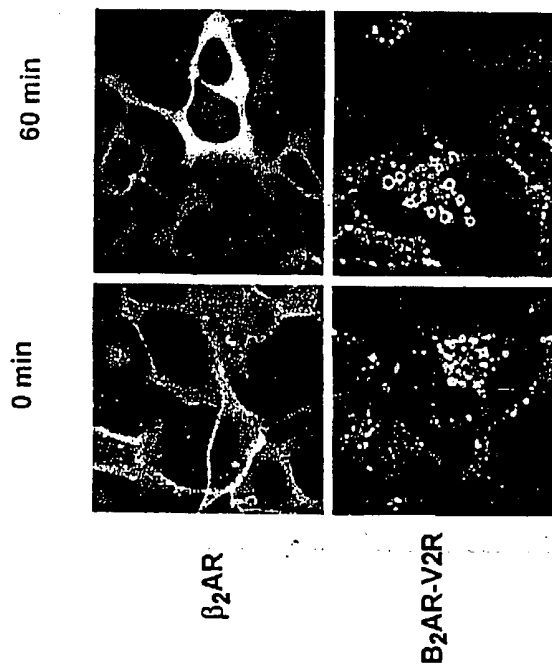


FIGURE 7A



REPLACEMENT SHEET



FIGURE 8A

|                             |   |
|-----------------------------|---|
| 1) V2R                      | CARGRTPPSLGPPQDESCTTASSSLAKDTSS   |
| 2) V2R-S362X                | CARGRTPPSLGPPQDESCTTA   |
| 3) V2R-SSSTSS/AAAAAA        | CARGRTPPSLGPPQDESCTTAAAAALAKDAAA  |
| 4) V2R-TSS/AAA              | CARGRTPPSLGPPQDESCTTASSSLAKDAAA   |
| 5) V24-SSS/AAA              | CARGRTPPSLGPPQDESCTTAAAAALAKDTSS  |
| 6) $\beta_2$ AR-V2R-SSS/AAA | CARGRTPPSLGPPQDESCTTAAAAALAKDTSS  |
| 7) $\beta_2$ AR             | CLRRSSLKAYGNGYSSNGNTGEQSGYHVEQEKENKLLCEDLP-<br>GTEDFVGHQGTVPDNDISQGRNCSTNDSLL           |
| 8) $\beta_2$ AR413-V2R10    | CLRRSSLKAYGNGYSSNGNTGEQSGYHVEQEKENKLLCEDLP-<br>GTEDFVGHQGTVPDNDISQGRNCSTNDSLLSSSLAKDTSS |
| 9) $\beta_2$ AR360-V2R10    | CLRRSSLKAYGNGYSSNGNTSSSLAKDTSS  |

FIGURE 8B

|       |   |
|-------|---|
| V2R   | NPWIYASFSSSVSSELRSLLCCARGRTPPSLGPPQDESCTTASSSLAKDTSS              |
| AAA-1 | -----AAA-----   |
| AAA-2 | -----AAA-----   |
| NTR-1 | NPILYNLVSANFRQVFLSTLACLCPGWRHRRKKRPTFSRKPNSSMSSNHAFSTSATRETLY     |
| AMAA  | -----A-AA-----  |
| AAA   | -----AAA-----   |
| OTR   | NPWIYMLFTGHLFHELVQRFLLCCSASYLKGRRLGETSASKKSNSSSFVLSHRSSQRSCSQPSTA |
| AAAA  | -----AAAA-----  |
| AAA-1 | -----AAA-----   |
| AAA-2 | -----AAA-----   |

# FIGURE 8C

REPLACEMENT SHEET



|       |   |
|-------|---|
| SPR   | NPIIYCCCLNDRFRLGFKHAFRCPCPFISAGDYEGLMKSTRYLQTOGVYKVSRLTETITVGAHEEPEDGPKATPSSLKLTSCSSRSDSKTMTESFSSNVLS |
| 383X  | -----X-----   |
| 355X  | -----X-----   |
| 325X  | -----X-----   |
| AAIAA | -----AA-AA-----   |
| APAA  | -----A-AA-----  |

REPLACEMENT SHEET



## FIGURE 9A

### Amino Acid Sequence of the Wild-Type Receptors

#### Amino acid sequence of the wild-type V2R

MLMASTTSAPVPGHPSLPSLPSNSSQERPLDTRDPLLARAELALLSIVFVAVALSNGLVLAA  
LARRGRRGHWAPIHVFIGHLCLADLAVALFQVLPQLAWKATDRFRGPDALCRAVKYLQMVG  
MYASSYMLAMTLDRHRAICRPMLAYRHGSGAHWNRPVLVAWAFSLLLSLPQLFIFAQRNV  
EGSGVTDWCWACFAEPWGRRTYVTWIALMVFVAPTLGIAACQVLIFREIHASLVPGPSPER  
GRRRRGRRTGSPGEGAHVSAAVAKTVRMTLVIVVVVLCWAPFFLVQLWAAWDPEAPLEGA  
PFVLLMLLASLNSCTNPWIYASFSSSVSSELRSLLCCARGRTPPSLGPQDESCTTASSSLA  
KDTSS

(Seq. ID No. 1)

## FIGURE 9B

#### Amino acid sequence of the wild-type $\beta_2$ AR

MGQPGNGSAFLLAPNRSHPDHDVTQQRDEVWVVGMIIVMSLIVLAIVFGNVLVITAIKF  
ERLQTVTNFYFITSACADLMGLAVVPFGAAHILMKMWTFGNFWCEFWTSIDVLCVTASIE  
TLCVIAVDRYFAITSPFKYQSLLTKNKARVILMVWIVSGLTSFLPIQMHWRATHQEAIN  
CYANETCCDFFTNQAYAIASSIVSFYVPLVIMVFVYSRVFQEAQRQLQKIDKSEGRFHVQN  
LSQVEQDGRGTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPPFFIVNIVHVIQDNLIRK  
EVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELLCLRRSSLKAYGNGYSSNGNTGEQSGY  
HVEQEKENKLLCEDLPGTEDFVGHQGTVPDNDISQGRNCSTNDSLL

(Seq. ID No. 2)

## FIGURE 9C

### Amino Acid Sequence of the Chimeric Receptors

#### Amino acid sequence of the $\beta_2$ AR-V2R chimera (Oakley et al.)

MGQPGNGSAFLLAPNRSHPDHDVTQQRDEVWVVGMIIVMSLIVLAIVFGNVLVITAIKF  
ERLQTVTNFYFITSACADLMGLAVVPFGAAHILMKMWTFGNFWCEFWTSIDVLCVTASIE  
TLCVIAVDRYFAITSPFKYQSLLTKNKARVILMVWIVSGLTSFLPIQMHWRATHQEAIN  
CYANETCCDFFTNQAYAIASSIVSFYVPLVIMVFVYSRVFQEAQRQLQKIDKSEGRFHVQN  
LSQVEQDGRGTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPPFFIVNIVHVIQDNLIRK  
EVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELL**CARGRTPPSLGPQDESCTTASSSLAK**  
DTSS

(Seq. ID No. 3)

\*shown in bold are the amino acids that were moved to the  $\beta_2$ AR to increase its affinity for arrestin.

REPLACEMENT SHEET



**FIGURE 10A**

**Amino acid sequence of the MOR-V2R chimera expressed from the pEArrB-1/MOR vector**

MDSSTGPGNTSDCSDPLAQASCSPAPGSWLNLSHVDGNQSDPCGLNRTGLG  
GNDSLCPQTGSPSMVTAITIMALYSIVCVVGLFGNFLVMYVIVRYTKMKTA  
TNIYIFNLALADALATSTLPPFQSVNYLMGTWPFGTILCKIVISIDYYNMFT  
SIFTLCTMSVDRIYAVCHPVKALDFRTPRNAKIVNVCNWILSSAIGLPVMF  
MATTKYRQGSIDCTLTFSHPTWYWENLLKICVFIFAFIMPILIITVCYGLM  
ILRLKSVRMLSGSKEKDRNLRRITRMVLVVAVFIVCWTPIHIVYIIKALI  
TIPETTFQTVSWHFCIALGYTNSCLNPVLYAFDENFKRCFREFCAAARGR  
TPPSLGPQDESCTTASSSLAKDTSS

(Seq. ID No. 4)

**FIGURE 10B**

**Amino acid sequence of the D1AR-V2R chimera expressed from the pEArrB-1/D1AR vector**

MAPNTSTMDEAGLPAERDFSFRILTACFLSLLILSTLLGNTLVCAAVIRFR  
HLRSKVTNFFVISLAVSDLLVAVLVMPWKAVAEIAGFWPFGSFCNIWVAFD  
IMCSTASILNLCVISVDRIYWAISSPFQYERKMTPKAAFILISVAWTLISVLI  
SFIPVQLSWHKAKPTWPLDGNFTSLEDTEDDNCDTRLRSRTYAISSSLISFY  
IPVAIMIVTYTSIYRIAQKQIRRI SALERA AVHAKNCQTTAGNGNPVECAQ  
SESSFKMSFKRETKVLKTL SVIMGVFVCCWLPFFISNCMPFCGSEETQPF  
CIDSITFDVFVWFGWANSSLNPIIYAFNADFQKAFSTLLGCYRLCAAARGR  
TPPSLGPQDESCTTASSSLAKDTSS

(Seq. ID No. 5)

REPLACEMENT SHEET



**FIGURE 10C**

**Amino acid sequence of the 5HT1AR-V2R chimera expressed from the pEArrB-1/5HT1AR vector**

MDVLSPGQGNNNTTSPAPFETGGNTTGISDVTVSYQVITSLLLGTLIIFCAV  
LGNACVVAIALERSLQNVANYLIGSLAVTDLMVSVLVLPMAALYQVLNKW  
TLGQVTCDLFIALDVLCTSSILHLCAIALDRYWAITDPIDYVNRKTPRRA  
AALISLTLWLGFLISIPMLGWRTPEDRSDPDACTISKDHGYTIYSTFGAF  
YIPLLLMLVLYGRIFRAARFRIRKTVKKVEKTGADTRHGASAPAPQPKSVN  
GESGSRNWRLGVESKAGGALCANGAVRQGDDGAALVIEVHRVGNSKEHLP  
LPSEAGPTPCAPASFERKNERNAAEAKRKMALARERKTVKTLGIIMGTFILC  
WLPFFIVALVLPFCESSCHMPTLLGAI  
INWLGYSNSLLNPVIYAYFNKDFQNAFKKIICKNFCAAARGRTPPSLGPQD  
**ESCTTASSSLAKDTSS**

(Seq. ID No. 6)

**FIGURE 10D**

**Amino acid sequence of the  $\beta$ 3AR-V2R chimera expressed from the pEArrB-1/ $\beta$ 3AR vector**

MAPWPHENSSSLAPWPDLPPTLAPNTANTSGLPGPVWEAALAGALLALAVLAT  
VGGNLLVIVAIWTPRLQTMNTNFVTSLAAADLMGLLVPPAATLALTGH  
WPLGATGCELWTSVDVLCVTASIETLCALAVDRYLAVTNPLRYGALVTKRC  
ARTAVVLVWVVSAAVSFAPIMSQWVRVGADAEARCHSNPRCCAFASNMPY  
VLLSSSVSFYLP LLVMLFVYARVFVATRQLRLLRGELGRFPPEESPAPS  
RSLAPAPVGTCPPEGVPACGRRPARLLPLREHRALCTLGLIMGTFTLCWL  
PFFLANVLRALGGPSLVPGPAFLALNWLGYSANSAFNPLIYCRSPDFRSAFR  
RLLCRCAAARGRTPPSLGPQDESCTTASSSLAKDTSS

(Seq. ID No. 7)

**FIGURE 10E**

**Amino acid sequence of the Edg1R-V2R chimera expressed from the pEArrB-1/Edg1R vector**

MGPTSVPLVKAHRSSVSDYVNYDIIVRHNYTGKLNISADKENSICKLTSV  
FILICCFIILENIFVLLTIWTKKFHRPMYYFIGNLALS DLLAGVAYTANL  
LLSGATTYKLTPAQWFLREGSMFVALSASFSLAIAIERIYITMLKMKLHN  
GSNNFRLFLLISACWVISLILGGLPIMGWNCISALSSCSTVLPLYHKHYIL  
FCTTVFTLLLLSIVILYCRYSLVRTRSRLTFRKNISKASRSSEKSLALL  
KTVIIVLSVFIACWAPLFILLLLDVGCKVKTC DILFRAEYFLVLAVLNSGT  
NPIIYTLTNKEMRRAFIRIMSCCKCAAARGRTPPSLGPQDESCTTASSSLA  
**KDTSS**

(Seq. ID No. 8)





REPLACEMENT SHEET

**FIGURE 11A**

**Nucleotide sequence of the  $\beta$ 2AR-V2R chimera**

atggggcaaccggaacggcagcgcccttcttgctggcacccaatagaagccatgcgccggacc  
acgacgtcacgcagcaaagggacgaggtgtgggtgggtgggcatgggcatcgatgtctctcat  
cgtcctggccatcgtgtttggcaatgtgctgggtcatcacagccattgccaaagtgcgagcgtctg  
cagacggtcaccaactacttcatcacttcaactggcctgtgctgatctgggtcatgggcctggcag  
tggtgccctttggggccgcccataattcttatgaaaatgtggacttttggcaacttctgggtgcga  
gttttggacttccattgatgtgctgtgctgcgtcacggccagcattgagaccctgtgcgtgatcgca  
gtggatcgctactttgccattacttcaactttcaagtaccagagcctgctgaccaagaataagg  
ccgggtgatcattctgatgggtgtggattgtgtcaggccttacctccttcttggccattcagat  
gcaactggtaccggggccaccaccaggaagccatcaactgctatgccaatgagacctgctgtgac  
ttcttcacgaaccaagcctatgccattgaccttccatcggtgctccttctacgttcccctgggtga  
tcatgggtcttcgtctactccagggtctttcaggaggccaaaaggcagctccagaagattgacaa  
atctgagggccgcttccatgtccagaaccttagccagggtggagcaggatgggcggacggggcat  
ggactccgcagatcttccaagttctgcttgaaggagcaciaaagccctcaagacggttaggcata  
tcatgggcaactttcacctctgctgggtgaccttcttcacgttaacattgtgcatgtgatcca  
ggataacctcatccgtaaggaagtttacatcctcctaaattggataggctatgtcaattctgggt  
ttcaatccccttatctactgcccggagcccagatttcaggattgccttcaggagcttctgtgcg  
cccggggacgcaccccaccagcctgggtccccaagatgagtcctgcaccaccgccagctcctc  
cctggccaaggacacttcatcgtga

(SEQ ID No. 9)

**FIGURE 11B**

**Nucleotide sequence of the MOR-V2R chimera**

atggacagcagcacccggcccagggaacaccagcgactgctcagaccccttagctcaggcaagtt  
gtccccagcacctgggtcctgggtcaacttgtcccacggtgatggcaaccagtcgatccatg  
cggctctgaaccgcaccgggcttggcggggaacgacagcctgtgccctcagaccggcagccctcc  
atgggtcacagccattaccatcatggccctctactctatcgtgtgtgtagtgggcctcttcggaa  
acttcctgggtcatgtatgtgattgtgaagatacaccaaaatgaagactgccaccaacatctacat  
tttcaaccttgctctggcagacgccttagcgaccagtagcactgaccttccagagtgtcaactac  
ctgatgggaacatggcccttcgggaaccatcctctgcaagatcgtgatctcaatagattactaca  
acatgttcaccagcatattcacctctgcaccatgagcgtggaccgctacattgctgtctgcca  
cccagtcaaaagccctggatttccgtaccccccgaaatgccaaaatcgtcaacgtctgcaactgg  
atcctctcttctgcccacggtctgctgtaatgttcatggcaaccacaaaatacaggcaggggt  
ccatagattgcacctcacgttctcccaccaacctggtagtgggagaacctgctcaaaatctg  
tgtctttatcttgcctttcatcatgcgatcctcatcatcactgtgtgttacggcctgatgatc  
ttacgactcaagagcgttcgcatgctatcgggctccaagaaaaggacaggaatctgcgcagga  
tccccggatgggtgctgggtgggtcgtgggtgtatttatcgtctgctggacccccatccacatcta  
cgtcatcatcaaagcgtgatcacgattccagaaaccacatttcagaccgttctcctggcacttc  
tgcattgctttgggttacacgaacagctgctgaatccagttctttacgccttctcctggatgaaa  
acttcaagcgtatgcttcagagagttctgcgcggcgccacggggacgcaccccaccagcctggg  
tccccaagatgagtcctgcaccaccgccagctcctccttggccaaggacacttcatcgtga

(SEQ ID No. 10)

REPLACEMENT SHEET



FIGURE 11C

Nucleotide sequence of the D1AR-V2R chimera

atggctcctaacttctaccatggatgaggcgggctgccagcggagagggatttctcctttc  
gcacctcacggcctgtttcctgtcactgtcactcctgtccactctcctgggcaatacccttgt  
ctgtgcggcgtcatccggtttcgacacctgaggtccaaggtgaccaacttctttgtcatctct  
ttagctgtgtcagatctcttgggtggtgtcctgggtcatgccctggaaagctgtggccgagattg  
ctggccttttggccctttgggtccttttgtaacatctgggtagcctttgacatcatgtgctctac  
ggcgtccattctgaacctctgctgtatcagcgtggacaggtactgggctatctccagccctttc  
cagtatgagaggaagatgacccccaaagcagccttcactcctgattagcgtagcatggactctgt  
ctgtccttatatccttcactccagtaacagctggcacaaggcaaagcccacatggccctt  
ggatggcaattttacctccctggaggacaccgaggatgacaactgtgacacaagggtgagcagg  
acgtatgccatttcactcgtccctcatcagcttttacatccccgtagccattatgatcgtcacct  
acaccagtatctacaggattgcccagaagcaaaccggcgcatctcagccttggagagggcagca  
gtccatgccaagaattgccagaccacgcaggttaacgggaaccccgctcgaatgcgccagctctg  
aaagtccctttaagatgtccttcaagagggagacgaaagtcttaagacgctgtctgtgatcat  
gggggtgtttgtgtgctgctggctccctttcttcatctcgaactgtatgggtgcccttctgtggc  
tctgaggagaccagccattctgcatcgattccatcaccttcgatgtgtttgtgtgggttgggt  
ggcggaattcttccctgaacccattatttatgcttttaatgctgacttccagaaggcgttctc  
aacctctttaggatgctacagactctgcgcggcgccagcggggacgcacccaccagcctgggt  
ccccaagatgagtcctgcaccaccgcagctcctccctggccaaggacacttcactgtga  
(SEQ ID No. 11)

FIGURE 11D

Nucleotide sequence of the 5HT1AR-V2R chimera

atggatgtgctcagccctgggtcagggcaacaacaccacatcaccaccgggtccctttgagaccg  
gcggcaacactactggatatctccgacgtgacgtcagctaccaagtgatcacctctctgctgct  
gggcaagctcatcttctgcgcgggtgctgggcaatgcgtgctggtggctgccatgccttggag  
cgctccctgcagaacgtggccaattatcttattggctctttggcggtcacgacctcatgggtgt  
cggtgttgggtgctgcccattggcgcgctgtatcaggtgctcaacaagtggacactgggcccagg  
aacctgcgaacctgttcacgcctcagcgtgctgtgctgcacctcatccatctgcacctgtgc  
gccatcgcgctggacaggtactgggcatcacggaccccatcgactacgtgaacaagaggacgc  
cccggcgcgcgctgcgctcatctcgtcacttggcttattggcttctcatctctatcccgcc  
catgctgggtggcgacccccggaagaccgctcggaccccgacgcatgcaccattagcaaggat  
catggctacactatctattccaccttggagctttctacatcccgctgctgctcatgctgggttc  
tctatgggcgcataattccgagctgcgcgcttccgcatccgcaagacggtcaaaaagggtggagaa  
gaccggagcggacaccgcctatggagcatctccgccccgcagcccaagaagagtgtgaatgga  
gagtcggggagcaggaactggaggctgggcgtggagagcaaggctgggggtgctctgtgcgcca  
atggcgcggtgaggcaagggtgacgatggcgccgacctggagggtgatcgagggtgcaccgagtggg  
caactccaaagagcacttgccctgcccagcagaggctggctcctacccttgtgccccgcctct  
ttcgagaggaaaaatgagcgcaacgcggaggcggaagcgcaagatggccctggcccagagagga  
agacagtgaagacgctgggcatcatcatgggcaccttcactcctctgctgggtgcccttcttcat  
cgtggctcttgttctgccccttctgcgagagcagctgccacatgccaccctgttgggcgcata  
atcaattggctgggctactccaactctctgcttaaccccgctcatttacgcatacttcaacaagg  
actttcaaaacgcgtttaagaagatcattaagtgttaacttctgcgcggcgccaggggacgcac  
cccaccagcctgggtcccccaagatgagtcctgcaccaccgcagctcctccctggccaaggac  
acttcactgtga  
(SEQ ID No. 12)

REPLACEMENT SHEET

FIGURE 11E



Nucleotide sequence of the  $\beta$ 3AR-V2R chimera

atggctccgtggcctcacgagaacagctctcttgcgccatggccggacctccccaccctggcgc  
ccaataccgccaacaccagtgggctgccaggggttcctgtgggaggcgccctagccggggccct  
gctggcgctggcggtgctggccaccgtgggaggcaacctgctggtcatcgctggccatcgccctgg  
actccgagactccagaccatgaccaacgtgttcgtgacttcgctggccgcagccgacctggtga  
tgggactcctggtggtgccgccggcgccaccttggcgctgactggccactggccgttggggcg  
cactggctgcgagctgtggacctcggtggacgtgctgtgtgtgaccgccagcatcgaaacctg  
tgccgcttggcggtggaccgctacctggctgtgaccaaccgctgcgttaaggcgccactggtca  
ccaagcgtgcgcccgacagctgtggtcctggtgtgggtcgtgtcgcccgcggtgtcgtttg  
gccccatcatgagccagtgggtggcgctagggggcgacgcccaggcgagcgctgccactccaac  
ccgcgctgctgtgccttcgcctccaacatgcctacgtgctgctgtcctcctcgctcctctt  
accttcctcttctcgatgctcttcgtctacgcgcgggttttcgtgggtggctacgcgccagct  
gcgcttgcgtgcgcggggagctggggcgcttccgcccaggagctcctcgccggcgccgtcgcg  
tctctggccccggccccgggtggggacgtgcgctccgcccgaagggtgcccgcctgcggccggc  
ggccccgcgcgcctcctgcctctccgggaacaccgggcccctgtgcaccttgggtctcatcatggg  
caccttcactctctgctggttgccttcttctggccaacgtgctgcgcgcctggggggcccc  
tctctagtcccgggccccgggttcttctggccctgaactggctagggtatgccaatctgccttca  
accgctcatctactgcgcagcccggaacttcgcagcgccctccgccgtcttctgtgccgctg  
cgcgccgcgaacggggacgcacccccaccagcctgggtccccaagatgagtcctgcaccaccgcca  
gtcctccttggccaaggacacttcatcgtga

(SEQ ID No. 13)

FIGURE 11F

Nucleotide sequence of the Edg1-V2R chimera

atggggcccaccagcgtcccgctggtcaaggcccaccgcagctcggtctctgactacgtcaact  
atgatcatcatcgctccggcattacaactacacgggaaagctgaatatcagcgccgacaaggagaa  
cagcattaaactgacctcggtggtgttcattctcatctgctgctttatcatcctggagaacatc  
tttgtcttgcgtgaccatttggaaaaccaagaaattccaccgacctatgtactattttattggca  
atctggccctctcagacctgttggcaggagtagcctacacagctaacctgctcttgcctggggc  
caccacctacaagctcactcccgcccagtggtttctgcgggaaggagtagtgggttggccctg  
tcagcctccgtgttcagtctcctcgccatcgccattgagcgctatatcacaatgctgaaaatga  
aactccacaacgggagcaataacttcgcctcttctgctaatcagcgccctgctgggtcatctc  
cctcatcctgggtggcctgcctatcatgggctggaactgcatcagtgcgctgtccagctgctcc  
accgtgctgcgcgtctaccacaagcactatctcttctgcaccacggctcttcactctgcttc  
tgctctccatcgctcattctgtactgcagaatctactccttgggtcaggactcggagccgcgcct  
gacgttccgcaagaacatttccaaggccagccgcagctctgagaagtcgctggcgctgctcaag  
accgtaattatcgctcctgagcgctcttcatcgctgctgggcaccgctcttcatcctgctcctgc  
tggatgtgggctgcaagggtgaagacctgtgacatcctcttcagagcggagtagtcttgggtgtt  
agctgtgctcaactccggcaccacccccatcatttacactctgaccaacaaggagatgcgtcg  
gccttcatccggatcatgtcctgctgcaagtgcgcggccgcacggggacgcacccccaccagcc  
tgggtccccaagatgagtcctgcaccaccgcccagctcctccttggccaaggacacttcatcgtg

a

(SEQ ID No. 14)